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# Health and Environmental Effects Profile for Acetonitrile

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# HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR ACETONITRILE

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16. ABSTRACT

The Health and Environmental Effects Profile for acetonitrile was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Acetonitrile has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for acetonitrile is 1.28 mg/day for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for acetonitrile is 100.

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# PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of $q_1^*$ (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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## LIST OF ABBREVIATIONS

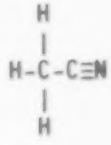
| | |
|---|---|
| ADI | Acceptable daily intake |
| BCF | Bioconcentration factor |
| BOD | Biological oxygen demand |
| BODT | Biological oxygen demand, theoretical |
| CAS | Chemical Abstracts Service |
| CS | Composite score |
| DMSO | Dimethyl sulfoxide |
| GC/MS | Gas chromatography/mass spectrometry |
| GI | Gastrointestinal |
| HCN | Hydrogen cyanide |
| HPLC | High performance liquid chromatography |
| i.p. | Intraperitoneal |
| $K_{oc}$ | Soil sorption coefficient |
| $K_{ow}$ | Octanol/water partition coefficient |
| $LC_{50}$ | Concentration lethal to 50% of recipients |
| $LD_{50}$ | Dose lethal to 50% of recipients |
| LOAEL | Lowest-observed-adverse-effect level |
| LOEL | Lowest-observed-effect level |
| MAC | Maximum allowable concentration |
| MED | Minimum effective dose |
| MTD | Maximum tolerated dose |
| NADPH | Nicotinamide adenine dinucleotide phosphate (reduced form) |
| NOAEL | No-observed-adverse-effect level |
| ppb | Parts per billion |
| ppm | Parts per million |

| | |
|---|---|
| RQ | Reportable quantity |
| s.c. | Subcutaneous |
| SD | Standard deviation |
| STEL | Short-term exposure limit |
| TLV | Threshold limit value |
| TWA | Time-weighted average |
| UV | Ultraviolet |
| WS | Water solubility |

# 1. INTRODUCTION

## 1.1. STRUCTURE AND CAS NUMBER

The common chemical name of this compound is acetonitrile, but it is also known by the synonyms methyl cyanide, cyanomethane, ethyl nitrile and ethanenitrile. The structure, molecular weight, and empirical formula for acetonitrile are as follows:



Molecular Weight: 41.05

Empirical Formula: $C_2H_3N$

The CAS Registry number for acetonitrile is 75-05-8.

## 1.2. PHYSICAL AND CHEMICAL PROPERTIES

Acetonitrile is a clear, colorless liquid with a sweet, ethereal odor (Smiley, 1981). Selected physical properties are listed below:

| | | |
|---|---|---|
| Freezing point: | -45.7°C | Smiley, 1981 |
| Boiling point: | 81.6°C (1 atm.) | Smiley, 1981 |
| Specific gravity, 20/4°C: | 0.786 | Smiley, 1981 |
| Vapor pressure, mm Hg: | | |
| at 7.7°C | 40 | Perry and Chilton, 1973 |
| at 15.9°C | 60 | Perry and Chilton, 1973 |
| at 20°C | 74 | Verschueren, 1983 |
| at 27.0°C | 100 | Perry and Chilton, 1973 |
| at 30°C | 115 | Verschueren, 1983 |
| Water solubility: | completely miscible | Smiley, 1981 |
| Nonaqueous solubility: | completely miscible in many common organic solvents | Smiley, 1981 |
| Evaporation rate: (butyl acetate = 100 | 579 | Smiley, 1981 |

| | | |
|---|---|---|
| Flash point: (Clev. open cup | 6°C | Smiley, 1981 |
| Refractive index, 20°C: | 1.3441 | Smiley, 1981 |
| Log $K_{ow}$: | -0.34 | Leo et al., 1971 |
| Conversion factor (air): | 1 mg/m³ = 0.586 ppm<br>1 ppm = 1.706 mg/m³ | Verschueren, 1983 |

Acetonitrile undergoes typical nitrile reactions, although it is one of the more stable nitriles. Typical nitrile reactions include acid or base catalyzed hydrolysis to form amides or acids, catalytic reduction to amines, and reactions with phenols to form ketones. Acetonitrile can be polymerized to the dimer and trimer, and has been telomerized with ethylene and copolymerized with alpha-epoxides. Its high dielectric strength and dipole moment make acetonitrile an excellent solvent for both inorganic and organic compounds including polymers (Smiley, 1981).

## 1.3. PRODUCTION DATA

All of the commercially produced acetonitrile manufactured in the United States in 1980 was produced as an isolated by-product from the manufacture of acrylonitrile by propylene ammoxidation (Smiley, 1981). The catalyst used during this process can determine the amount of acetonitrile formed, but the ratio of acrylonitrile:acetonitrile is ~35:1. The acetonitrile, recovered as the water azeotrope, is dried and purified by distillation (Smiley, 1981). Not all of the by-product acetonitrile formed has commercial demand; therefore, the excess crude acetonitrile is usually incinerated (Groet, 1978).

SRI (1984) lists DuPont (Beaumont, TX; Memphis, TN) and Sohio Chemical (Lima, OH), a subsidary of the Standard Oil Co. (Ohio), as current producers of acetonitrile. In addition to DuPont and Sohio, USITC (1984) identifies

the J.T. Baker Co. and an unnamed company (name withheld by request) as producers during 1983. All of the acrylonitrile manufacturers probably produce acetonitrile as a by-product; the acrylonitrile manufacturers include DuPont, Sohio, Monsanto and American Cyanamid (SRI, 1984). DuPont and Sohio have the capacity to produce ~18 million pounds of acetonitrile annually (Smiley, 1981). Domestic production of acetonitrile in recent years has been reported as follows (USITC, 1981, 1982, 1983, 1984):

| Year | Production (million of lbs.) |
|---|---|
| 1983 | 22.3 |
| 1982 | 20.9 |
| 1981 | 70.8 |
| 1980 | 25.2 |

Current import and export data are not available.

1.4. USE DATA

A percentage breakdown of the end uses of acetronitrile is not available; however, acetonitrile is primarily used commercially and industrially as a solvent. Its largest use is for the separation of butadiene from $C_4$ hydrocarbons by extractive distillation. It is widely used as a recoverable reaction medium solvent, especially in the manufacture of pharmaceuticals. Because of its superior solvency for polymers, it is used as a specialty solvent for spinning fibers and for casting and molding of plastic materials. Acetonitrile is used widely in spectrophotometry and electrochemistry as a highly-purified grade product; a growing solvent use is in HPLC for the detection of materials such as pesticide residues in the ppb range (Smiley, 1981). Lithium batteries use acetonitrile as a solvent to decrease $SO_2$ vapor pressures and increase electrolyte solubility and ionic conductivity (Gu and Bennion, 1978). Acetonitrile is an excellent

solvent for the extraction of fatty acids from animal and vegetable oils (Hawley, 1977; Gergel and Revelise, 1952).

Smiley (1981) cited the following additional applications of acetonitrile: as a catalyst and ingredient of transition-metal complex catalysts; a variety of uses in the photographic industry; extraction and refining of copper and by-product ammonium sulfate; used in dyeing textiles and in coating compositions; as a stabilizer for chlorinated solvents; specialty uses in perfume production; and as a chemical intermediate.

## 2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

The fate of acetonitrile in the environment will depend on its ability to undergo chemical, photochemical and biological reactions and to be transported or partitioned from one environmental matrix into another. The individual fate processes are discussed below.

### 2.1. WATER

2.1.1. Hydrolysis. Brown et al. (1975) reported that the hydrolysis rate constant for acetonitrile in an aqueous solution of pH 10 is $1.195 \times 10^{-8}$ $M^{-1}$ $sec^{-1}$. Assuming a constant pH 10 (pOH 4), the half-life for this process would be >18,000 years. At 100°C and 2-5% NaOH, the acetonitrile hydrolysis rate constant is 0.345 $min^{-1}$ (Linetskii and Serebryakov, 1965), but this has no environmental significance. Hydrolysis data in neutral solutions were not located.

2.1.2. Oxidation. Anbar and Neta (1967) reported that the rate constant for the reaction of acetonitrile with hydroxyl radicals in aqueous solution of pH 9 at room temperature is $2.1 \times 10^{6}$ $M^{-1}$ $sec^{-1}$; assuming an environmental hydroxyl radical concentration of $10^{-17}$ M, a half-life of 1042 years can be calculated. Dorfman and Adams (1973) reported a similar hydroxyl radical rate constant of $3.5 \times 10^{6}$ $M^{-1}$ $sec^{-1}$.

Reaction of acetonitrile with other aqueous oxidants has not been reported. No other evidence is available to suggest that oxidation has environmental significance.

2.1.3. Photolysis. The absorption maximum for acetonitrile in the UV range is <160 nm (Silverstein and Bassler, 1967); therefore, the direct photolysis of acetonitrile in the aquatic environment is not expected to occur. No data are available regarding the potential occurrence of photosensitized photolysis.

2.1.4. Microbial Degradation. Placak and Ruchhoft (1947) examined the degradation of acetonitrile by activated sludge in BOD tests using a concentration of 490 ppm and batch aeration; 17% was degraded in 24 hours, while the 5-day BOD was 96% of theoretical.

Ludzack et al. (1958, 1959) tested the biodegradation of acetonitrile in Ohio River water and in aged sewage by measuring $CO_2$ evolution. Degradation in the river water occurred at a faster rate than in the sewage; the 12-day BODT in river water was 40% but only 20% in the sewage. Acclimatization of microorganisms was examined by redosing, and degradation was determined to occur 5 times more rapidly after acclimation was achieved. The effect of temperature on biodegradation was also studied; degradation at 5°C required 2.5-5 times longer than at 20°C. Ludzack et al. (1961) examined the degradation of acetonitrile by activated sludge in a continuous feed test at 22-25°C; 82-94% BOD was removed during 4 weeks of test operation. Results of anaerobic digestion tests with acetonitrile suggested that this is not an effective means of removing the compound from wastewaters (Ludzack et al., 1961).

Using the Japanese MITI test, Sasaki (1978) reported that acetonitrile is "well-biodegradable," meaning that oxygen consumption is >30% in 2 weeks. Thom and Agg (1975) reported that acetonitrile should be degradable by biological sewage treatment with appropriate acclimatization. Mimura et al. (1969) isolated the bacterium, Corynebacterium nitrilophius, from activated sludge and determined that this microorganism was capable of assimilating acetonitrile. Kelly et al. (1967) found virtually no degradation of acetonitrile by nitrogenase of Azotobacter chroococcum.

Firmin and Gray (1976) used a species of Pseudomonas capable of using acetonitrile as a sole carbon source to show that acetonitrile undergoes

direct enzymatic hydrolysis. The authors used [2-$^{14}$C]-labeled acetonitrile to postulate the following metabolic pathway: acetonitrile → acetamide → acetate → tricarboxylic acid-cyclic intermediates (citrate, succinate, fumarate, malate, glutamate, etc.). Ludzack et al. (1961) observed high levels of nitrates in effluents from activated sludge degrading acetonitrile.

2.1.5. Transport. The transport of acetonitrile in the aquatic environment will depend on the ability of the compound to volatilize, to adsorb to particulate organic matter and sediment, and to bioaccumulate in aquatic organisms.

2.1.5.1. **VOLATILIZATION** -- Hine and Mookerjee (1975) reported that a dilute aqueous solution of acetonitrile at equilibrium at 25°C has a concentration in the water-phase to concentration in the gas-phase ratio of 891:1. The inverse of this ratio, $1.1 \times 10^{-3}$, is the unitless Henry's Law constant. Conversion to units, using an RT value of $2.4 \times 10^{-2}$ m$^3$-atm/mol (where R is the gas constant and T is temperature in K), yields a Henry's Law constant of $2.6 \times 10^{-5}$ m$^3$-atm/mol. This value of Henry's Law constant indicates that volatilization is probably significant for most environmental bodies of water, although the rate may not be rapid (Lyman et al., 1982). Volatilization half-lives (first order kinetics) can be predicted from this Henry's Law constant by using the U.S. EPA's EXAMS computer simulation (Burns et al., 1981); half-lives from typical environmental water bodies are as follows:

| Water Body | Half-life |
|---|---|
| pond | 11 days |
| river | 6 days |
| oligotrophic lake | 34 days |
| eutrophic lake | 36 days |

2.1.5.2. ADSORPTION -- Experimental data considering the adsorption of acetonitrile to particulate organic matter and sediment in water were not located; however, the complete water solubility of acetonitrile suggests that partitioning from the water column to sediments or particulates is probably not significant.

2.1.5.3. BIOACCUMULATION -- Experimental bioconcentration data with respect to aquatic organisms were not located. The complete water solubility and low log $K_{ow}$ (-0.34) (Leo et al., 1971) of acetonitrile suggest that bioaccumulation in aquatic organisms will not have environmental significance. The BCF of an organic compound may be estimated from the WS and from the $K_{ow}$ by the following equations:

$$\log BCF = 2.791-0.564 \log WS \text{ (in ppm)} \quad \text{(Kenaga and Goring, 1980)} \quad (2\text{-}1)$$

$$\log BCF = 0.76 \log K_{ow} - 0.23 \quad \text{(Veith et al, 1980)} \quad (2\text{-}2)$$

Assuming WS is $10^6$ ppm, the BCF value calculated from both equations is 0.3.

2.2. AIR

The atmospheric chemical removal processes include reaction of the target chemical with hydroxyl or other free radicals, reaction with ozone, and photolytic transformations (Cupitt, 1980). The rate constant for the gas-phase reaction of acetonitrile with hydroxyl radicals has been experimentally determined by Harris et al. (1981) to be $0.494 \times 10^{-13}$ cm$^3$ molecule$^{-1}$ sec$^{-1}$ at 24.2°C; in the temperature range 298-424°K (25-151°C), the rate constant was described by the equation $k=5.86 \times 10^{-13}$ exp (-1500 cal mole$^{-1}$/RT). From this rate constant data, Harris et al.

(1981) calculated the tropospheric destruction rate of acetonitrile at 25°C to be ~$5 \times 10^{-7}$ $sec^{-1}$ for a mean concentration of $10^7$ hydroxy radicals/$cm^3$ in a moderately polluted troposphere; this rate yielded a tropospheric lifetime of ~20 days. In a more average atmosphere of $10^6$ hydroxy radicals/$cm^3$, the lifetime will be 10 times longer. Guesten et al. (1981) reported the rate constant for the reaction between hydroxy radicals and acetonitrile in the gas-phase to be ~$0.2 \times 10^{-13}$ $cm^3$ $molecule^{-1}$ $sec^{-1}$ at room temperature, which is in reasonably good agreement with Harris et al. (1981). The Arrhenius activation energies of ~1500 cal $mole^{-1}$, as determined by Harris et al. (1981), indicate that the reaction proceeds largely or entirely by abstraction of a hydrogen atom.

Harris et al. (1981) also determined in laboratory studies that the rate of reaction of acetonitrile with ozone was relatively slow, with a rate constant of $\leq 1.5 \times 10^{-19}$ $cm^3$ $molecule^{-1}$ $sec^{-1}$. In a typical atmosphere of $10^{12}$ ozone molecules/$cm^3$, a half-life of $\geq$54 days can be calculated from this rate constant.

The reaction rate constant between singlet oxygen and acetonitrile is reported to be $2.4 \times 10^{-16}$ $cm^3$ $molecule^{-1}$ $sec^{-1}$ (Graedel, 1978); this predicts an atmospheric half-life of >5000 years. Reaction data were not located for other atmospheric radical species.

Dimitriades and Joshi (1977) reported on the reactivity of acetonitrile as measured in an EPA smog chamber with 22 blacklights, 7 sunlamps, 4 ppm of the test compound and 0.2 ppm $NO_x$. Acetonitrile was found to be unreactive with respect to ozone yield. The average rate of disappearance of acetonitrile was measured as 0.02% per hour, or 100 times slower than that measured for propane. Kagiya et al. (1975) measured the photochemical decomposition rate of acetonitrile (300-2000 ppm) in air saturated with

water in a reaction cell irradiated with a mercury lamp. No degradation was observed; however, when 2000 ppm chlorine gas was added to the cell, the decomposition rate was 1.32% per second. Reaction between chloride radicals and acetonitrile in the ambient atmosphere is not thought to be significant in relation to hydroxyl radical reaction (Arijs et al., 1983).

The absorption maximum for acetonitrile in the UV range is <160 nm (Silverstein and Bassler, 1967); therefore, the direct photolysis of acetonitrile in the ambient atmosphere is not expected to occur.

The physical atmospheric removal processes include dissolution (wet deposition), adsorption on aerosol particles and dry deposition (Cupitt, 1980). The complete water miscibility of acetonitrile suggests that dissolution into clouds and raindroplets may occur with subsequent removal by rainfall. Adsorption on aerosol particles is not expected to have any importance, as Cupitt (1980) suggested that vapor-phase adsorption is a reasonable mechanism only for compounds with saturation vapor pressures of $\leq 10^{-7}$ mm Hg. Dry deposition is also not expected to be significant.

2.3. SOIL

2.3.1. Microbial Degradation. DiGeronimo and Antoine (1976) isolated Nocardia rhodochrus LL100-21 from barnyard soil and demonstrated that the microorganism was capable of using acetonitrile as a source of carbon and nitrogen. A decrease in acetonitrile content within the culture medium was correlated with an increase of acetamide and acetic acid; ammonia was also detected. Under the test conditions, the initial concentration of acetonitrile was reduced by 14% in 3 hours and by 52% in 8 hours. Crude cell-free extracts were also found to degrade acetonitrile by an enzymatic hydrolysis mechanism that was determined to be inducible. Kuwahara et al. (1980) found that Aeromonas sp. BN 7013 could be grown using acetonitrile as

a nitrogen source; the microorganism was isolated from soil. Harper (1977) isolated a strain of the fungus, Fusarium solani, from soil and found that cell-free extracts, containing the nitrilase enzyme, were capable of enzymatically hydrolyzing acetonitrile.

Data from the study by Ludzack et al. (1958; 1959) (see Section 2.1.4.) indicated that acetonitrile underwent significant biodegradation in river water.

2.3.2. Chemical Degradation. Experimental data regarding the chemical degradation of acetonitrile in soil were not located in the available literature as cited in the Appendix.

2.3.3. Transport. Experimental data regarding the leaching of acetonitrile in soil were not located in the available literature as cited in the Appendix. The complete WS and $K_{ow}$ of acetonitrile predict that it will be highly mobile and, therefore, easily leached in soil. A $K_{oc}$ for acetonitrile may be estimated from the following equations using the WS and the $K_{ow}$:

$$\log K_{oc} = 3.64-0.55 \log WS \text{ (in ppm) (Kenaga and Goring, 1980)} \quad (2-3)$$

$$\log K_{oc} = 0.544 \log K_{ow} + 1.377 \text{ (Kenaga and Goring, 1980)} \quad (2-4)$$

Assuming WS is $10^6$ ppm, the $K_{oc}$ values calculated from equations 2-3 and 2-4 are 2 and 15 , respectively. The soil sorption can also be predicted from molecular topology and quantitative structure-activity relationships by a method presented by Sabljic (1984), which predicts a $K_{oc}$ value of 10.

The volatility of acetonitrile from soil surfaces has not been studied. Chiou et al. (1980) experimentally examined the evaporation of acetonitrile

from stainless steel planchets into still air at 23-25°C; the rate of evaporation of acetonitrile ($3.69 \times 10^{-5}$ g/cm²-sec) was found to be 37.3 times more rapid than that of water. While evaporation from soil is more complex, these data, coupled with the prediction of low soil sorption and the high relative vapor pressure of acetonitrile, suggest that volatilization will have some significance in the ambient environment.

## 2.4. SUMMARY

In the aquatic environment, microbial degradation and volatilization appear to be the significant fate and transport processes. At 20-25°C, the half-life in natural waters can be estimated to be ~1-2 weeks from biodegradation data in river water (Ludzack et al., 1958) and from volatility estimations (Burns et al., 1981). This relatively rapid removal from water seems to be confirmed by the lack of monitoring data in the aquatic environment (Section 3.1.). Acetonitrile is not expected to bioaccumulate in aquatic organisms.

Reaction with hydroxyl radicals appears to be the major removal process of acetonitrile in the atmosphere; a tropospheric lifetime of ~20 days has been calculated for moderately polluted air (Harris et al., 1981). In more typical air, however, removal by hydroxy radicals will not be as rapid and reaction with ozone and removal in rainfall (by dissolution) may contribute more to the overall atmospheric removal of acetonitrile.

Data pertaining to the fate of acetonitrile in natural soil were not located in the available literature as cited in the Appendix; however, laboratory data indicate that acetonitrile is susceptible to significant microbial degradation. Based on the physical properties of acetonitrile, high soil mobility and easy leaching can be predicted. Significant evaporation from soil surfaces may occur.

## 3. EXPOSURE

### 3.1. WATER

The U.S. EPA STORET Data Base contains no monitoring data on acetonitrile. No other aquatic monitoring data were located.

Contamination of water can occur from discharges of manufacturing and use facilities (Gruber, 1975). In soils, acetonitrile may be susceptible to leaching into groundwater. Atmospheric acetonitrile may be transported to surface water by rainfall.

### 3.2. FOOD

Pertinent data regarding the monitoring of acetonitrile in food were not located in the available literature as cited in the Appendix.

### 3.3. INHALATION

Becker and Ionescu (1982) monitored the lower troposphere near ground levels in both urban and rural locations and detected acetonitrile in concentrations of 2-7 ppb by volume using GC/MS. Acetonitrile has also been reported to be present in the upper stratosphere (Arijs et al., 1983).

Emission of acetonitrile into the air has been reported by several authors. Gruber (1975) noted that fugitive emissions from manufacturing facilities can release acetonitrile into the air; emissions from industrial use facilities are also possible. Hawthorne and Sievers (1984) detected acetonitrile vapor emissions from shale oil wastewaters; volatilization from the aquatic environment may also be an emission source. Graedel (1978) listed acetonitrile emission sources including industrial sources, synthetic rubber manufacturing and turbine engines. Schuchmann and Laidler (1972) suggested that acetonitrile may be emitted in automobile exhaust gas, while Kadaba et al. (1978) detected acetonitrile in tobacco smoke.

## 3.4. DERMAL

Pertinent data regarding dermal exposure to acetonitrile were not located in the available literature as cited in the Appendix.

# 4. PHARMACOKINETICS

## 4.1. ABSORPTION

Available data on the rate or extent of uptake or absorption of acetonitrile are limited to inhalation exposures. In a group of 16 human subjects who were cigarette smokers, an average of 74% absorption of acetonitrile was measured when the smoke was held in the mouth for two seconds and was not inhaled. When the subjects were classified by the number of cigarettes smoked per day, a slight but statistically significant ($p<0.05$) inverse correlation was noted between the smoking rate and the extent of acetonitrile absorption (Dalhamn et al., 1968a). When the cigarette smoke was inhaled into the lungs, absorption of acetonitrile increased to 91% (Dalhamn et al., 1968b).

The only other quantitative study on absorption is that conducted by Pozzani et al. (1959a), in which three beagle dogs were exposed for 4 hours to acetonitrile vapor at an air concentration of 16,000 ppm (27,296 mg/m$^3$). After ~1 hour, blood cyanide concentrations were 33-53 µg/100 mℓ blood. Blood cyanide levels peaked after ~3 hours (305-433 µg/100 mℓ blood) and were somewhat reduced at the end of the 4-hour exposure period (266-291 µg/100 mℓ blood). The authors did not discuss this pattern of absorption but noted one "analytical artifact" during the elimination phase of this study. Given the small number of animals used in this study and possible problems in the analytical technique, these data cannot be used to derive a rate coefficient for absorption. Nonetheless, the data indicate that acetonitrile is absorbed rapidly upon inhalation and suggest that the dogs may have been nearing steady-state blood concentrations at 3-4 hours after exposure.

Absorption of acetonitrile by the GI tract and skin as well as the lungs can be inferred from other pharmacokinetic data discussed below and from the toxicity data discussed in Chapter 5.

## 4.2. DISTRIBUTION

Distribution appears to be quite extensive, with acetonitrile and its metabolic products transported throughout the major organs and tissues of the body by the blood. A metabolite, hydrocyanic acid, was found in high levels in the brain, heart, kidney and spleen of rats exposed to acetonitrile by inhalation. (Haguenoer, 1975a). Willhite (1983) has studied distribution in the Syrian Golden Hamster after oral ingestion or i.p. injection of acetonitrile in water. Cyanide and thiocyanate levels in acetonitrile treated animals were measured in the blood, liver, brain and kidney; results are summarized in Table 4-1. Ahmed and Farooqui (1982) presented distribution data in rats after ingestion of an oral 2460 mg/kg dose of acetonitrile in saline. Levels of cyanide in the liver were 16 µg/g, in the kidney, 102 µg/g and in the brain, 28 µg/g. In rats exposed to 2800 ppm (4701 mg/m³) or 25,000 ppm (41,973 mg/m³) acetonitrile by inhalation, chemical analysis of organs showed that the mean concentration of acetonitrile in the muscle was 136 µg/100 g of tissue and 2438 µg/100 g of kidney tissue. Free hydrogen cyanide in the liver was 27 µg/100 g and in the spleen was 400 µg/100 g tissue.

Following fatal poisoning of a human exposed by inhalation to acetonitrile, Dequidt et al. (1974) reported that mononitriles (specifically acetonitrile) were uniformly distributed in the internal organs, and cyanide metabolites were found in the spleen, stomach and skin. Smaller amounts of metabolites were found in the liver, lungs, kidneys, heart, brain, muscle, intestines and testes. Grabois (1955) also reported that high levels of

TABLE 4-1

Cyanide and Thiocyanate Concentrations in Tissues of Acetonitrile-Treated Hamsters[a,b]

| Compound/Dose | Route | Whole Blood | | Liver | | Brain | | Kidney | |
|---|---|---|---|---|---|---|---|---|---|
| | | Cyanide | Thiocyanate | Cyanide | Thiocyanate | Cyanide | Thiocyanate | Cyanide | Thiocyanate |
| Distilled water/ 0.5 mL | oral | 0.2 ± 0.05 | 11.0 ± 1.0 | 0.1 ± 0.04 | 25.0 ± 3.3 | 0.2 ± 0.1 | 6.7 ± 1.2 | 0.6 ± 0.3 | 41.8 ± 2.7 |
| Acetonitrile/ 100 mg/kg | oral | 0.9 ± 0.4 | 38.0 ± 11.4 | 1.8 ± 1.1 | 43.1 ± 7.2 | 0.5 ± 0.3 | 10.0 ± 1.2 | 0.7 ± 0.3 | 72.8 ± 14.1 |
| 200 mg/kg | oral | 0.6 ± 0.3 | 37.9 ± 7.9 | 1.4 ± 0.4 | 65.7 ± 20.3 | 1.4 ± 0.8 | 7.2 ± 2.7 | 0.6 ± 0.3 | 70.4 ± 14.7 |
| 300 mg/kg | oral | 3.5 ± 2.3 | 56.3 ± 6.3 | 3.1 ± 1.6 | 63.4 ± 5.6 | 0.7 ± 0.3 | 11.7 ± 1.7 | 1.6 ± 0.9 | 95.2 ± 7.1 |
| 400 mg/kg | oral | 27.4 ± 21.6 | 102.9 ± 15.7 | 34.0 ± 30.4 | 118.1 ± 26.7 | 17.0 ± 15.0 | 13.1 ± 3.8 | 11.9 ± 8.9 | 135.2 ± 16.0 |
| Distilled water/ 0.5 mL | i.p. | 0.7 ± 0.6 | 7.0 ± 2.6 | 0.3 ± 0.2 | 22.2 ± 2.0 | 0.3 ± 0.1 | 5.1 ± 2.3 | 0.5 ± 0.4 | 40.2 ± 3.9 |
| Acetonitrile/ 100 mg/kg | i.p. | 2.2 ± 0.8 | 35.0 ± 17.4 | 1.1 ± 0.6 | 42.8 ± 10.2 | 1.3 ± 0.7 | 2.3 ± 1.0 | 1.4 ± 0.6 | 65.8 ± 18.7 |
| 200 mg/kg | i.p. | 1.7 ± 0.7 | 41.2 ± 9.9 | 2.9 ± 0.6 | 52.6 ± 6.7 | 0.9 ± 0.5 | 7.2 ± 1.8 | 1.0 ± 0.5 | 75.1 ± 11.5 |
| 300 mg/kg | i.p. | 3.1 ± 4.0 | 51.5 ± 9.0 | 2.6 ± 2.7 | 54.9 ± 19.5 | 1.8 ± 1.3 | 8.5 ± 2.9 | 1.9 ± 1.1 | 80.5 ± 20.0 |
| 400 mg/kg | i.p. | 41.6 ± 11.5 | 126.0 ± 54.0 | 72.2 ± 23.1 | 109.4 ± 7.8 | 20.8 ± 5.0 | 11.2 ± 4.6 | 38.4 ± 10.8 | 109.6 ± 17.0 |

[a]Source: Willhite, 1983

[b]Values are expressed as nmol/g organ wet weight or nmol/mL blood and represent the mean ± S.E.M. for five animals. Concentrations of cyanide and thiocyanate were determined 2.5 hours after distilled water or acetonitrile.

cyanide ion were found in the blood (796 µg/100 mℓ), urine (215 µg/100 mℓ), kidney (204 µg/100 mℓ), spleen (318 µg/100 mℓ) and lungs (128 µg/100 mℓ), but not in the liver of a human following fatal inhalation exposure.

In a second experiment reported by Haguenoer et al. (1975a), rats inhaled 2800 ppm (4701 mg/m³) acetonitrile for 2 hours/day for 5 days. Necropsy revealed that all organs contained acetonitrile and free hydrocyanic acid in the range of 96.0-286.9 and 53-990 µg/100 g tissue, respectively.

Willhite and Smith (1981) presented data on tissue concentrations of cyanide in mice that were injected with acetonitrile. Injection of 175 mg/kg i.p. in saline produced 47.8 nmol/g cyanide in liver and 13.4 nmol/g cyanide in brain.

Haguenoer et al. (1975b) reported on the distribution of acetonitrile in Wistar rats injected i.p. with doses of 2340, 1500 and 600 mg/kg. Urine was collected and assayed (Section 4.4.). At necropsy on day 11 after injection, tissue analysis showed no important differences in acetonitrile, hydrogen cyanide, thiocyanates or cyanocobalamine content between treated and control animals.

In a previous study in rats using a single i.p. injection of 780 mg acetonitrile, Dequidt and Haguenoer (1972) found acetonitrile in all organs analyzed (93.4-174.9 mg/100 g). Levels of combined hydrogen cyanide ranged from a low in the liver (359 µg/100 g) to high levels in the spleen (1347 µg/100 g), stomach (1757 µg/100 g) and skin (1045 µg/100 g). Levels of free hydrogen cyanide ranged from 17 µg/100 g tissue in the liver to 347 µg/100 g tissue in the spleen.

## 4.3. METABOLISM

The effects of exposure to acetonitrile are due in part to release of the cyanide ion from the metabolism of the parent compound, acetonitrile (Zeller et al., 1969; Amdur, 1959; Pozzani et al., 1959a). Acetonitrile is metabolized to acetaldehyde and inorganic cyanide, which is further oxidized to thiocyanate (Silver et al., 1982). McKee et al. (1962) found that after absorption, nitriles may be metabolized to an α-cyanohydrin or to inorganic cyanide, which is oxidized to thiocyanate. The cyanide group may also be converted into a carboxylic acid derivative and ammonia, or may be incorporated into cyanocobalamine. Ionic cyanide also reacts with carboxyl groups and with disulfide groups (Silver et al., 1982).

Haguenoer et al. (1975a,c) found that the internal organs of rats contained thiocyanates, cyanohydrins and cyanocobalamines after having been injected i.p. with varying levels of acetonitrile, ranging from 600-2340 mg/kg.

Several lines of evidence implicate cytochrome P-450 dependent enzyme systems in the metabolism of nitriles to cyanide (Abreu and Ahmed, 1980; Contessa and Santi, 1973; Ohkawa et al., 1972). Acetonitrile is metabolized more slowly than other similar nitriles, which may explain the delayed onset of acute toxicity symptoms (Hartung, 1962). Signs of toxicity produced by metabolism of acetonitrile are those of cyanide and thiocyanate poisoning (NIOSH, 1978). It is possible that intestinal bacteria may contribute to the level of cyanohydrin intermediates due to localized nitrile metabolism in the GI tract (Szabo and Reynolds, 1975).

Within groups of hamsters given the same dose of acetonitrile, there was a large variation in the concentration of metabolites in organs and tissues (Willhite, 1983). This large variation in cyanide concentration of various

tissues had been documented previously by these same authors (Willhite and Smith, 1981). Tissue concentrations from the most recent Willhite (1983) study are presentec in Section 4.2. The overall pattern of biotransformation was similar, whether acetonitrile was administered orally or i.p. A consistent increase in concentrations of cyanide and thio- cyanate was seen in all tissues.

In vitro biotransformation of acetonitrile was examined using hamster liver and microsomal preparations. As seen in Table 4-2, the increase in the concentration of metabolites was not proportional to the increase in acetonitrile concentration, indicating that metabolic processes were becoming saturated at high acetonitrile concentrations.

## 4.4. EXCRETION

Acetonitrile is eliminated by exhalation of unchanged compound and urinary excretion of free and bound hydrogen cyanide or acetonitrile (Haguenoer et al., 1975a,c). Silver et al. (1982) reported that 11.8 and 4.4% of the dose administered to rats by the oral and i.p. routes, respectively, were excreted as thiocyanate in the urine within 24 hours after administration.

Haguenoer et al. (1975a,b) found that bound hydrogen cyanide as thiocyanates, cyanohydrins and cyanocobalamine predominated in the urine, along with some free hydrogen cyanide. Low levels of unchanged acetonitrile were found in urine up to 4 days after exposure to acetonitrile, and cyanate excretion continued for 11 days following i.p. administration.

Acetonitrile has been found in the morning urine of cigarette smokers. Concentrations ranging from 2.2-20 µg/100 ml urine for heavy smokers have been found (McKee et al., 1962).

TABLE 4-2

Cyanide and Thiocyanate Production from Acetonitrile *In Vitro*[a]

| Preparation | Acetonitrile (mmol/mℓ) | Cyanide (nmol/g) | Thiocyanate (nmol/g) |
|---|---|---|---|
| Liver slice[b] | 0.0 | 0.0 ± 0.0 | 28.9 ± 4.2 |
| | 0.003 | 0.3 ± 0.1 | 47.7 ± 10.9 |
| | 0.03 | 0.7 ± 0.4 | 94.3 ± 21.6 |
| | 0.37 | 16.2 ± 6.0 | 219.8 ± 28.0 |
| Microsomes[c] | 0.0 | 0.7 ± 0.2 | NM |
| | 0.003 | 2.4 ± 0.3 | NM |
| | 0.03 | 6.3 ± 1.5 | NM |
| | 0.37 | 40.5 ± 3.0 | NM |
| | 3.78 | 136.6 ± 6.0 | NM |

[a]Source: Willhite, 1983

[b]Hamster-liver slices were incubated for 2.5 hours at 37°C in pH 7.4 Krebs-Ringer biocarbonate buffer containing 1.0 mg D-glucose/mℓ. Each value represents the mean ± S.E.M. for six experiments. Cyanide and thiocyanate liberation are expressed as nmol/g wet liver per 2.5 hours.

[c]Hamster-liver microsomes were incubated for 30 minutes at 37°C in pH 7.4 Krebs-Ringer biocarbonate buffer. The microsomal suspension was equivalent to 250 mg liver and 10.0 µmol NADPH were added at the start. Each value represents the mean ± S.E.M. for six experiments. Cyanide production is expressed as nmol/g wet liver per 30 minutes.

NM = Not measured

# 5. EFFECTS

## 5.1. CARCINOGENICITY

Studies on the carcinogenicity of acetonitrile were not located in the available literature as cited in the Appendix. The NTP (1985) has approved acetonitrile for testing but the tests have not yet been initiated.

## 5.2. MUTAGENICITY

Florin et al. (1980) tested acetronitrile on four strains of Salmonella typhimurium and noted no mutagenic activity. The Federal Register (1982) reported that NTP is conducting additional mutagenicity tests on acetonitrile. No published reports of these studies have been located in the literature.

Brown and Donnelly (1984) reported mutagenic activity in acidic, basic and neutral extracts from a waste stream of a petrochemical plant where acetonitrile was being purified. The waste stream contained 3.46% acetonitrile, 0.92% acetamide, 0.09% "R-OH" and 0.5% "heavy ends." The chemical composition of the fractions were not identified.

Acetonitrile has been found to be unacceptable as a solvent for use in mutagenicity assays (Arimoto et al., 1982; Kawalek and Andrews, 1980; Maron et al., 1981).

## 5.3. TERATOGENICITY

As summarized in Table 5-1, oral exposure of pregnant Syrian Golden hamsters during the early primitive streak of embryogenesis (day 8 of gestation) caused severe abnormalities in fetuses (Willhite, 1983). Doses ranged from 100-400 mg/kg, given to the dams as a single oral dose of acetonitrile in water. At the highest oral dose, signs of maternal intoxication were observed and well developed after 2.5 hours. Intubation with 300-400 mg/kg acetonitrile was associated with a significant increase in the numbers of

TABLE 5-1

Teratogenic Effects of Oral Administration of Acetonitrile on Hamster Embryonic Development[a,b]

| Compound/Dose | No. Animals Treated | No. Animals Died | No. Litters | Implantation Sites | Resorptions No. (%) (95% limit) | Living Fetuses | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Normal No. (%) | Abnormal No. (%) (95% limit) | Abnormalities | | | Average Weight of Fetuses (g ± SD) |
| | | | | | | | | Exencephaly | Encephalocoele | Ribs | |
| Distilled water/ 0.5 mL | 6 | 0 | 4 | 44 | 0 (0) (0.00-0.081) | 44 (100) | 0 (0) (0.00-0.081) | 0 | 0 | 0 | 2.23 ± 0.32 |
| Acetonitrile/ 100 mg/kg | 6 | 0 | 5 | 62 | 4 (6) (0.017-0.157) | 56 (90) | 2 (10) (0.004-0.120) | 0 | 2 | 0 | 1.89[c] ± 0.30 |
| Acetonitrile/ 200 mg/kg | 6 | 0 | 4 | 43 | 5 (12)[d] (0.03-0.26) | 38 (100) | 0 (0) (0.00-0.093) | 0 | 0 | 0 | 1.91[c] ± 0.28 |
| Acetonitrile/ 300 mg/kg | 6 | 1 | 5 | 65 | 0 (0)[e] (0.00-0.056) | 53 (81) | 12 (19)[d,e] (0.09-0.31) | 1 | 1 | 10 | 1.76[c] ± 0.38 |
| Acetonitrile/ 400 mg/kg | 12 | 4 | 8 | 98 | 22 (22)[d,e] (0.14-0.32) | 62 (82) | 14 (18)[d] (0.10-0.29) | 0 | 1 | 13 | 1.87[c] ± 0.34 |
| Acetonitrile/ 400 mg/kg plus $Na_2S_2O_3$/ 300 mg/kg | 12 | 0 | 11 | 144 | 4 (3)[e] (0.007-0.070) | 131 (94) | 9 (6)[f] (0.029-0.119) | 0 | 0 | 5 | 1.88[c] ± 0.27 |

[a]Source: Willhite, 1983

[b]Pregnant hamsters were given an oral dose of distilled water, acetonitrile in distilled water or the designated dose of acetonitrile and multiple i.p. injections of sodium thiosulfate (300 mg/kg every 120 minutes over a 10-hour period) on the morning of day 8 of gestation. The animals were killed on day 15 of gestation.

[c]Significantly different from control at $p<0.05$. In all comparisons of fetal weights, the total number of live fetuses was used for statistical purposes.

[d]Significantly different from control at $p<0.05$.

[e]Significantly different from preceding dose at $p<0.05$.

[f]Significantly different from treatment with 400 mg/kg acetonitrile alone at $p<0.05$.

malformed offspring. At the 200 or 400 mg/kg levels, there was a significant increase in fetal resorptions. A dose of 100 mg/kg acetonitrile failed to elicit any signs of maternal toxicity, but two litters had abnormal fetuses. At the 400 mg/kg level, in two of the five litters, one or more malformed offspring was present, or the entire litter was resorbed. Congenital malformations following treatment with acetonitrile were not considered to be the result of maternal intoxication, seen at the higher dose levels, because grossly malformed animals were recovered from dams that failed to show overt signs of nitrile intoxication. There was a significant decrease in the average fetal body weight associated with intubation of acetonitrile when compared with controls given water in the same manner. No consistent body weight changes were seen in the dams.

Intraperitoneal injection of thiosulfate before intubation with 400 mg/kg acetonitrile resulted in complete protection from acetonitrile poisoning and mortality and significantly reduced the number of malformed offspring and resorptions at this dose level. No significant differences in body weight gain were seen after this treatment. Results of this study are summarized in Table 5-1. These results suggested that in vivo liberation of cyanide from acetonitrile was responsible for the production of malformations (Willhite, 1983).

Inhalation of 5000 (8394 mg/m$^3$) or 8000 (13,431 mg/m$^3$) ppm acetonitrile for 60 minutes on day 8 of gestation was associated with these same malformations (Table 5-2). Inhalation of 1800 (3022 mg/m$^3$) or 3800 (6379 mg/m$^3$) ppm for 60 minutes did not induce fetal malformations or signs of toxicity in the dams. One dam exposed to 3800 ppm (6379 mg/m$^3$) showed dyspnea, tremors, hypersalivation, ataxia and hypothermia after 60 minutes of exposure, and died 3 hours later. The other five hamsters showed no

TABLE 5-2

Teratogenic Effects of Exposure to Acetonitrile Vapors on Hamster Embryonic Development[a,b]

| Compound/ Concentration | No. Animals Exposed | No. Animals Died | No. Litters[c] | Implantation Sites | Resorptions No. (%) (95% Limit)[d] | Living Fetuses | | | | | | Average Weight of Fetuses (g ± SD) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Normal No. (%) | Abnormal No. (%) (95% limit)[d] | Abnormalities | | | | |
| | | | | | | | | Exencephaly | Encephalocoele | Ribs | Other[e] | |
| Dehumidified air/ 10 ℓ/min | 10 | 0 | 10 | 121 | 3 (2) (0.005-0.071) | 118 (100) | 0 (0) (0.00-0.031) | 0 | 0 | 0 | 0 | 1.28 ± 0.17 |
| Acetonitrile/ 1800 ppm | 6 | 0 | 5 | 65 | 0 (0) (0.00-0.056) | 65 (100) | 0 (0) (0.00-0.056) | 0 | 0 | 0 | 0 | 1.25 ± 0.23 |
| Acetonitrile/ 3800 ppm | 6 | 1 | 4 | 49 | 2 (4) (0.004-0.140) | 47 (100) | 0 (0) (0.00-0.076) | 0 | 0 | 0 | 0 | 1.37 ± 0.26 |
| Acetonitrile/ 5000 ppm | 6 | 1 | 5 | 61 | 8 (13)[f] (0.05-0.25) | 47 (89) | 6 (11)[f,g] (0.04-0.23) | 2 | 2 | 2 | 1 | 1.20 ± 0.21 |
| Acetonitrile/ 8000 ppm | 12 | 3 | 9 | 120 | 5 (4) (0.013-0.095) | 86 (75) | 29 (25)[f,g] (0.17-0.35) | 13 | 14 | 9 | 1 | 1.19[h] ± 0.22 |
| Acetonitrile/ 8000 ppm plus $Na_2S_2O_3$/ 300 mg/kg, i.p. | 9 | 0 | 8 | 92 | 4 (7) (0.011-0.108) | 84 (95) | 4 (5)[i] (0.112-0.113) | 0 | 0 | 4 | 0 | 1.36[h] ± 0.16 |

[a]Source: Willhite, 1983

[b]Pregnant hamsters were exposed to either dehumidified air or to the designated concentration of acetonitrile in dehumidified air for 1 hour on the morning of day 8 of gestation. In those cases where pregnant hamsters were given an i.p. injection of sodium thiosulfate, the animals received 300 mg/kg every 120 minutes over a 10-hour period. The animals were killed on day 14 of gestation.

[c]The difference between litter number, dead animals and total treated nonpregnant animals

[d]95% confidence interval for the proportion of abnormal fetuses or the proportion of resorptions for each treatment

[e]Includes renal agenesis or ectopia cordis

[f]Significantly different from control at $p<0.05$.

[g]Significantly different from preceding concentration at $p<0.05$.

[h]Significantly different from control $p<0.05$. In all comparisons of fetal weights, the total number of live fetuses was used for statistical purposes.

[i]Significantly different from exposure to 8000 ppm acetonitrile alone at $p<0.05$.



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signs of intoxication at this exposure level and their offspring were normal. At 5000 ppm (8394 mg/m³), all animals were irritated and salivated excessively. One hamster suffered dyspnea, hypothermia and tremors after 60 minutes exposure, and died 5 hours later. Six abnormal fetuses were found in two litters taken from other animals exposed at this level. Malformations seen were exencephaly, encephalocoele and rib fusions.

Four hamsters exposed for 60 minutes to 8000 ppm (13,431 mg/m³) showed signs of acute toxicity and three died 1.5 hours after termination of exposure. Histopathological studies failed to reveal any changes in liver, kidney and lungs. Offspring of these dams were afflicted with severe axial skeletal disorders in five of the nine surviving litters. Average fetal body weights were also decreased when compared with litters from mothers exposed only to chamber air. One fetus showed extrathoracic ectopia cordis with accompanying defects in the sternum (a rare syndrome). A significant increase was seen in the number of abnormal fetuses at the 5000 (8394 mg/m³) or 8000 (13,431 mg/m³) ppm level when compared with control animals exposed to chamber air. In addition, there was a significant increase in the number of malformed offspring at 5000 ppm (8394 mg/m³) when compared with the lower level of exposure [3800 ppm (6379 mg/m³)], which was also true when 8000 (13,431 mg/m³) and 5000 (8394 mg/m³) ppm levels were compared. Intraperitoneal injections of thiosulfate reduced malformations, but irritation by the vapor was still evident as shown by conjunctivitis and red mucous membranes.

Intraperitoneal injection of 100-400 mg/kg acetonitrile failed to produce signs of poisoning in hamsters. One fetus taken from a dam given 100 mg/kg exhibited craniorachischisis (total myeloschisis), gastroschisis and apparent retrocession of the maxilla (Table 5-3). One fetus from a dam

TABLE 5-3

Teratogenic Effects of Parenteral Administration of Acetonitrile on Hamster Embryonic Development[a,b]

| Compound/Dose | No. Animals Treated | No. Animals Died | No. Litters[c] | Implantation Sites | Resorptions No. (%) (95% limit) | Living Fetuses | | | | | | Average Weight of Fetuses (g ± SD) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Normal No. (%) | Abnormal No. (%) (95% limit) | Abnormalities | | | | |
| | | | | | | | | Exencephaly | Encephalocoele | Ribs | Other[d] | |
| Distilled water/ 0.5 ml | 6 | 0 | 6 | 71 | 0 (0) (0.00-0.51) | 71 (100) | 0 (0) (0.00-0.051) | 0 | 0 | 0 | 0 | 1.20 ± 0.17 |
| $Na_2S_2O_3$/ 300 mg/kg | 7 | 0 | 6 | 72 | 3 (4) (0.008-0.117) | 69 (100) | 0 (0) (0.00-0.053) | 0 | 0 | 0 | 0 | 1.27[e] ± 0.19 |
| Acetonitrile/ 100 mg/kg | 6 | 0 | 6 | 69 | 0 (0) (0.00-0.053) | 67 (97) | 2 (3) (0.003-0.101) | 1[f] | 1 | 1 | 1 | 1.24 ± 0.22 |
| Acetonitrile/ 200 mg/kg | 6 | 0 | 5 | 61 | 0 (0) (0.00-0.059) | 60 (98) | 1 (2) (0.0004-0.088) | 0 | 0 | 0 | 1 | 1.27[e] ± 0.18 |
| Acetonitrile/ 300 mg/kg | 5 | 0 | 5 | 64 | 0 (0) (0.00-0.057) | 64 (100) | 0 (0) (0.00-0.057) | 0 | 0 | 0 | 0 | 1.28[e] ± 0.16 |
| Acetonitrile/ 400 mg/kg | 12 | 0 | 12 | 150 | 6 (4) (0.014-0.085) | 146 (97) | 4 (3) (0.007-0.067) | 1[f] | 1 | 1 | 1 | 1.30[e] ± 0.17 |
| Acetonitrile/ 400 mg/kg plus $Na_2S_2O_3$/ 300 mg/kg | 12 | 0 | 10 | 118 | 6 (5) (0.018-0.108) | 111 (99) | 1 (1) (0.0002-0.049) | 0 | 0 | 1 | 0 | 1.22 ± 0.16 |

[a]Source: Willhite, 1983

[b]Pregnant hamsters were given an i.p. injection of distilled water, sodium thiosulfate in distilled water (300 mg/kg every 120 minutes over a 10-hour period), acetonitrile in distilled water or the designated dose of acetronitrile and sodium thiosulfate on the morning of day 8 of gestation. The animals were sacrificed on day 14 of gestation.

[c]The difference between litter number, dead animals and total treated represents nonpregnant animals.

[d]Includes quadrilateral meromelia with lobster claw, rachischisis and exopthalmia.

[e]Significantly different from control at $p<0.05$. In all comparisons of fetal weights, the total number of live fetuses was used for statistical purposes.

[f]Animals were afflicted with craniorachischisis totalis and gastroshchisis.

treated with 200 mg/kg acetonitrile exhibited quadrilateral meromelia with lobster claw. Associated with 400 mg/kg acetonitrile was cranioschisis occulta with encephalocoele, craniorachisis or lumbrosacral rachischisis (myeloschisis) in one fetus in each of four different litters. Overall, there was no significant increase in numbers of malformed fetuses or resorptions compared with controls injected intraperitoneally with water. A significant increase in average fetal body weight was associated with i.p. injections at the 200-400 mg/kg level of acetonitrile. The authors were not clear as to the relevance of this finding. Thiosulfate treatment did not affect the number of malformed fetuses or resorptions when doses were given i.p. and there was no significant change in average maternal body weight gain when compared with i.p. injected ($H_2O$) control animals.

In an unpublished study conducted for Monsanto Company by IRDC (1981), groups of 25 female Charles River COBS rats were treated by gavage with acetonitrile in water at dosages of 0, 125, 190 and 275 mg/kg/day on days 6-19 of gestation. Day 0 of gestation was defined as the day on which evidence of mating was found. The dams were killed on day 20 of gestation. Maternal toxicity, as evidenced by death of two dams, reduced body weight gain and emaciation of two dams, was observed at 275 mg/kg/day. The cause of death of the two high-dose dams could not be determined upon necropsy. The high-dose group also had an increased mean number of early resorptions, increased mean postimplantation loss and decreased mean number of viable fetuses. These differences were not observed at 125 or 190 mg/kg/day and were not statistically significant when compared with concurrent controls, but were significant when compared with historic controls. No differences were observed with respect to mean numbers of total implantation, corpora

lutea, fetal sex ratio or fetal body weight in any of the treated groups compared with controls. No increased incidences of fetal malformations were observed. There was a slight increased incidence of unossified sternebrae in all treated groups compared with the concurrent control groups but the incidence was not different when compared with historic controls.

Crowe (1973) reported no teratogenic effects in newborn pigs after administration of acetonitrile to pregnant sows. A full report of the study was not available for this review.

## 5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects have not been located in the available literature as cited in the Appendix.

## 5.5. CHRONIC TOXICITY

Pozzani et al. (1959a) investigated the subchronic toxicity of acetonitrile in rats, dogs and monkeys exposed by inhalation. Wistar rats (140-200 g) (treated: 15/sex/exposure level; controls: two sets of 15/sex) were exposed to 0, 166 (279 mg/m³), 330 (554 mg/m³) or 655 ppm (1099 mg/m³) acetonitrile vapor for 7 hours/day, 5 days/week for a total of 90 days. Data concerning liver, kidney and body weight were recorded, along with observations of the histological appearance of kidney, liver and lung. Other tissues from a few rats exposed to 655 ppm (1099 mg/m³) were examined histologically; hematocrit and hemoglobin values were also determined for five females in the 655 (1099 mg/m³) ppm group and for controls.

No statistically significant changes or histological effects were observed in groups exposed to 166 (279 mg/m³) or 330 ppm (554 mg/m³) when compared with controls. One animal of the 29 control animals studied developed a lung granuloma. At the 166 ppm (279 mg/m³) level, 2/28 rats

exhibited lung changes such as histiocyte clumps in alveoli, atelectasis, bronchitis or pneumonia. At the 330 ppm (554 mg/m³) level, 3/26 rats also exhibited these lung changes.

Histological changes observed at the 655 ppm (1099 mg/m³) level were transitory pulmonary lesions including "alveolar capillary congestion and focal edema, often accompanied by bronchial inflammation, desquamation and hypersecretion of mucus," found in 10 of the 27 males and females. Other observations at the 655 ppm (1099 mg/m³) level were tubular cloudy swelling of the kidneys (8/27) and central cloudy swelling of the liver (7/27). Although the incidence of these lesions in controls were not reported, the authors stated that the incidences were statistically significant compared with controls ($p<0.05$). At 655 ppm (1099 mg/m³), focal cerebral hemorrhage occurred in one of five brains examined, but no lesions were found in samples of adrenals, pancreas, spleen, testes or trachea.

Three adult male mongrel dogs were exposed to 350 ppm (558 mg/m³), 7 hours/day, 5 days/week for 91 days (Pozzani et al. 1959a). These animals exhibited pulmonary abnormalities including focal emphysema, atelectasis and proliferation of the alveolar septa. There was transient depression of hematocrit and hemoglobin values, but no significant deviation in erythrocyte count. No control data were provided.

In the same study (Pozzani et al., 1959a), three male rhesus monkeys were exposed to 350 ppm (588 mg/m³) acetonitrile 7 hours/day, 5 days/week for 91days. An additional series of one or two rhesus monkeys (per exposure level) were given 330 (554 mg/m³), 660 (1108 mg/m³) or 2510 ppm (4214 mg/m³) for up to 99 days. The animal exposed to 2510 ppm died from severe pulmonary effects on the second day of exposure. Two animals exposed to 660 ppm (1108 mg/m³) died on day 23 and 51. All of the six animals exposed to

330-660 ppm (554-1108 mg/m³) had brain hemorrhages (focal dural or subdural hemorrhages of tissues adjacent to the superior sagittal sinus, or slight to moderate hemorrhage of the superior and inferior sagittal sinuses). Renal effects were cloudy swelling of convoluted tubules in five of the animals. There was some evidence of focal emphysema and proliferation of alveolar septa in the lung. At 660 ppm (1108 mg/m³), two monkeys had poor coordination. One monkey exposed to 330 ppm (554 mg/m³) "exhibited overextension reflexes and considerable excitability." Six monkeys had pulmonary abnormalities similar to those described for the dogs. At 350 ppm (554 mg/m³), small discrete caseous nodules developed in the lungs of two of the three monkeys exposed.

## 5.6. OTHER RELEVANT INFORMATION

$LD_{50}$ or $LC_{50}$ values are summarized in Table 5-4. Acute oral exposure in rats produces labored breathing, ataxia, cyanosis and coma (Kimura et al., 1971). Skin and eye irritation were similar to those produced by acetone (Smyth and Carpenter, 1948).

Acute studies have been performed by Smyth and Carpenter (1948), Kimura et al. (1971), Pozzani (1959a,b), Marine et al. (1932, 1933), and Spence and Marine (1932). Human and animal studies have suggested that the toxicity of aliphatic nitriles is correlated with their ability to liberate cyanide as a result of metabolism of the parent compound (Ahmed and Farooqui, 1982). Effects of nitrile poisoning include duodenal ulcers, nuclear changes in neurons and satellite spinal ganglia, thyroid hypermia and hyperplasia, neurogenic bladder dysfunction and adrenal apoplexy (Szabo and Seyle, 1972; van Breeman and Hiraoka, 1961; Spence and Marine, 1932; Kreiss et al., 1980; Szabo et al., 1980, 1982). In general, cyanide antagonists are not as effective in combating cyanide poisoning when it is due to metabolism of

TABLE 5-4

$LD_{50}$ or $LC_{50}$ Values for Acetonitrile[a]

| Route | Species | $LD_{50}$ or $LC_{50}$ | Reference |
|---|---|---|---|
| Oral | rat | 3.8 g/kg | Smyth and Carpenter, 1948 |
| Oral | rat | 8.27 mℓ/kg (~6525 mg/kg) | Pozzani et al., 1959b |
| Oral | rat | 3.6 g/kg | Arbuzov, 1968 |
| Oral | rat | 3200 mg/kg | Zeller et al., 1969 |
| Oral | rat | 2.46 g/kg[b] | Union Carbide Corp., 1970 |
| Oral | rat | 160-3100 mg/kg[c] | Kimura et al., 1971 |
| Oral | rat | 4.4 mℓ/kg[d] (~3458 mg/kg) | Kimura et al., 1971 |
| Oral | rat | 2460 mg/kg | Ahmed and Farooqui, 1982 |
| Oral | mice | 6.550 mmol/kg (~269 mg/kg) | Tanii and Hashimoto, 1984 |
| Inhalation | rat | 16,000 ppm (4 hours) | Pozzani et al., 1959a |
| Inhalation | rat | 26.9 mg/ℓ ($LC_{50}$)(4 hours) | Pozzani et al., 1959b |
| Inhalation | mice | 2693 ppm ($LC_{50}$) | Willhite, 1981 |
| Inhalation | guinea pig | 5655 ppm (14 hours) | Pozzani et al., 1959a |
| Inhalation | rabbit | 2828 ppm (4 hours) | Pozzani et al., 1959a |
| i.p. | rat | 0.92 g/kg | Arbuzov, 1968 |

TABLE 5-4 (cont.)

| Route | Species | $LD_{50}$ or $LC_{50}$ | Reference |
|---|---|---|---|
| i.p. | rat | 0.85 and 0.95 mℓ/kg | Pozzani et al., 1959b |
| i.p. | mice | 400 mg/kg | Zeller et al., 1969 |
| i.p. | mice | 500 mg/kg | NIOSH, 1978 |
| i.p. | mice | 175 mg/kg | Willhite and Smith, 1981 |
| Dermal | rabbit | 3.9 g/kg | Smyth and Carpenter, 1948 |
| Dermal | rabbit | 1250 mg/kg | NIOSH, 1978 |
| s.c. | rat | 3.6 g/kg | Arbuzov, 1968 |

[a]Source: Modified from Hartung, 1982

[b]Value obtained from Union Carbide

[c]14-day-old more sensitive than young adults

[d]Older adults

nitriles (Ahmed and Farooqui, 1982). These authors found that the toxic expressions of aliphatic nitriles depended not only upon cyanide liberation, but also on their chemical structure.

Several case studies of acute exposure in humans have been reported. Grabois (1955) described a fatality and several cases of accidental poisoning in workers exposed to acetonitrile vapor; this incident was discussed further by Amdur (1959). Dequidt et al. (1972, 1974) reported the fatal exposure of a photographic laboratory worker to acetonitrile.

In a study designed to assess toxicant interactions based on the assumption of dose additivity, Pozzani et al. (1959b) determined the oral $LD_{50}$s and inhalation $LC_{50}$s of binary mixtures of acetonitrile with acetone, carbon tetrachloride, toluene, propylene oxide or epichlorohydrin. Greater than additive potency was noted with mixtures of acetonitrile and acetone for both oral (3.6 times greater) and inhalation (2.7 times greater) toxicity. In a similar study, Smyth et al. (1969) reported greater than additive potency for mixtures of acetonitrile with either acetone (3.6 times greater) or dioxane (3.2 times greater) based on determinations of oral $LD_{50}$s.

Carbon tetrachloride pretreatment may reduce the acute toxic potency of acetonitrile. After carbon tetrachloride pretreatment, mice that were subsequently exposed to 5000 ppm (8394 mg/m$^3$) acetonitrile by inhalation for 1 hour or 575 mg/kg by the i.p. route showed sharply reduced fatalities (Willhite, 1981; Willhite and Smith, 1981). Without carbon tetrachloride pretreatment, deaths from inhalation were 10/10; with pretreatment, deaths were reduced to 2/10. With the injection dose, after pretreatment, deaths were 0/10; without carbon tetrachloride pretreatment, deaths were 7/10. Sodium thiosulfate was also protective, and sodium nitrite was less

protective (Willhite, 1981). Tanii and Hashimoto (1984) found that an oral dose of 9.96 nmol/kg bw of acetonitrile (in water) killed 8/10 mice pretreated with olive oil, whereas 0/10 mice pretreated with carbon tetrachloride died. Arbuzov (1975) reported that acetonitrile-induced lung edema was prevented by compounds that blocked N-cholino-receptors or by glucocorticoids or SH group donors, but $NaNO_2$ and $Na_2S_2O_3$ did not prevent edema.

Arbuzov (1972) found that pulmonary edema resulting from a lethal subcutaneous dose of acetonitrile to mice was decreased by preliminary blocking of the β-adrenoreceptors.

When used as a solvent vehicle in an assay for glutathione S-transferase activity of rat liver, concentrations of 0.021-0.63 mol/ℓ acetonitrile inhibited enzymatic conjugation of styrene oxide at a low level and, to a lesser extent, conjugation of benzo[a]pyrene 4,5-oxide and 1,2-dichloro-4-nitrobenzene (Aitio and Bend, 1979). In an earlier study, Aitio (1977) found no inhibition of monooxygenase activity in rat hepatic microsomes. In in vitro assays of microsomal mixed function oxidase activity, Kawalek and Andrews (1980) found inhibition that was statistically significant when acetonitrile (1.22 mmol/mℓ) was added in combination with aniline, aminopyrine and benzo[a]pyrene.

Using ascites sarcoma BP8 cells cultured in vitro, Pilotti et al. (1975) found no inhibition on cell culture growth rate when cells were exposed to 1 mM acetonitrile. Using isolated rat heptacytes in vitro (Sauers et al., 1980), acetonitrile had the least effect on dimethylphenobarbital N-demethylation when compared with acetone, propylene glycol, ethanol and dimethylsulfide being used as drug vehicles.

Thelestam et al. (1980) investigated the effect of tobacco smoke compounds on permeability of membranes of human lung fibroblasts and found nitriles to be completely inactive.

## 6. AQUATIC TOXICITY

### 6.1. ACUTE TOXICITY

The toxicity of acetonitrile was determined in 96-hour tests using bluegill sunfish, Lepomis macrochirus, fathead minnows, Pimephales promelas and guppies, Lebistes reticulatus (Henderson et al., 1960). Tests with fathead minnows were conducted using hard (380 mg $CaCO_3$/ℓ) and soft water (20 mg $CaCO_3$/ℓ), while tests in other species were conducted using soft water. In fathead minnows, 24-, 48- and 96-hour $LC_{50}$ values were 1150, 1050 and 1000 mg acetonitrile/ℓ in hard water and 1050, 1000 and 1000 mg acetonitrile/ℓ in soft water. Water hardness did not appear to significantly influence acetonitrile toxicity. The 24-, 48- and 96-hour $LC_{50}$ values were all 1850 mg/ℓ for bluegills and 1650 mg/ℓ for guppies. In toxicity tests using the medaka, Oryzias latipes, Tonogai et al. (1982) reported that 24- and 48-hour $LC_{50}$ values were not <1000 mg acetonitrile/ℓ. In the golden orfe, Leuciscus idus, test, Juhnke and Luedemann (1978) reported 48-hour $LC_0$, $LC_{50}$ and $LC_{100}$ values of 3900, 5850 and 6240 mg acetonitrile/ℓ from one laboratory and values of 4330, 7050 and 8670 mg/ℓ, respectively, from a second laboratory. Acetonitrile appears to have a low toxicity in fish species.

In the freshwater cruatacean, Daphnia magna, toxic concentrations were also quite high. Bringmann and Kuhn (1977, 1982) reported that the 24-hour $LC_{50}$ value was >10,000 mg acetonitrile/ℓ in the water flea, D. magna.

### 6.2. CHRONIC EFFECTS

Exposure to acetonitrile at 100 mg/ℓ for up to 4 weeks had no apparent toxic or lethal effects on adult bluegill sunfish, L. macrochirus (Henderson et al., 1960). Treatment did not cause excess sloughing of the external

mucous layer of fish. Chronic tests were conducted to determine if pollutants imparted tastes to fish flesh, but no taste was detected in acetonitrile-exposed bluegills.

### 6.3. PLANT EFFECTS

The effects of acetonitrile on cell-multiplication in the blue-green algae, Microcystis aeruginosa, and the green algae, Scenedesmus quadricauda, were examined by Bringmann and Kuhn (1978). Toxicity threshold concentrations causing the first detectable inhibition of cell multiplication were 520 and 7300 mg acetonitrile/ℓ, respectively, for the blue-green and green algae. The blue-green algae was ~14 times more sensitive to acetonitrile than the green algae.

### 6.4. RESIDUE

Pertinent data regarding residues of acetonitrile in aquatic organisms were not located in the available literature as cited in the Appendix. Aceto- nitrile could not be detected organoleptically by a panel of 12 chemists and biologists in treated fish but the fish flesh was cooled before testing (Henderson et al., 1960).

### 6.5. OTHER RELEVANT INFORMATION

The toxicity threshold concentrations of acetonitrile, causing decreased cell multiplication, were 680 and 1810 mg/ℓ in the bacteria, Pseudomonas putida, and the protozoan, Entosiphon sulcatum, respectively (Bringmann and Kuehn, 1980).

Collins and Knowles (1983) reported that the bacteria, Nocardia rhodochrous, was able to grow in acetonitrile at 1.03 g/ℓ. Apparently, the bacteria used acetonitrile as a source of both carbon and nitrogen.

## 7. EXISTING GUIDELINES AND STANDARDS

### 7.1. HUMAN

NIOSH (1978) recommended a TWA-TLV of 20 ppm (34 mg/m³) for acetonitrile. OSHA listed an exposure level for acetonitrile of 40 ppm (70 mg/m³) (Code of Federal Regulations, 1981).

ACGIH (1984) lists a TWA-TLV of 40 ppm (70 mg/m³) with a skin notation, indicating that there is potential contribution to the overall exposure by the dermal route, and a STEL of 60 ppm (105 mg/m³), derived from human and animal exposure (ACGIH, 1980). Australia, Belgium, the Federal Republic of Germany, Finland, the Netherlands, Switzerland and Yugoslovia have established levels at 70 mg/m³ (40 ppm), determined as an 8-hour TWA. The USSR set an MAC of 10 mg/m³ (6 ppm) and Rumania set an MAC of 50 mg/m³ (29 ppm) and an average concentration limit of 30 mg/m³ (18 ppm) with a "skin" notation (NIOSH, 1978).

### 7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of acetonitrile were not located in the available literature as cited in the Appendix.

## 8. RISK ASSESSMENT

Acetonitrile has not been tested for carcinogenicity. Only one mutagenicity study has been conducted, which yielded negative results in the spot test using Salmonella typhimurium (Florin et al., 1980). The report by Brown and Donnelly (1984) of significant mutagenic activity in acid, base and neutral extracts from a petrochemical plant waste stream that contained 3.46% acetonitrile is difficult to interpret because the chemical composition of the fractions was not identified.

Data were available indicating that acetonitrile is fetotoxic in rats and teratogenic in hamsters. In an unpublished study conducted by IRDC (1981) for Monsanto Company, rats were given daily gavage doses of 125, 190 and 275 mg/kg/day on days 6-19 of gestation. At the highest dose level, maternal toxicity and embryotoxic effects were reported. No teratogenic effects were reported at any dose level.

Willhite (1983) presented data on teratogenicity in the Syrian Golden hamster (100-140 g) from exposures of the dam to acetonitrile by inhalation, ingestion or i.p. injection, during the early primitive streak of embryogenesis. Inhalation of acetonitrile by the dams produced significantly increased incidences ($p<0.05$) of fetal abnormalities (exencephaly, encephalocoele, rib and other skeletal malformations) at the levels of 5000 ppm (8394 mg/m$^3$) (1-hour exposure on day 8 of gestation). The dams exhibited vapor irritation and showed excessive salivation, but histopathological examination of the liver, kidneys and lungs showed no abnormalities. Dams exposed to 3800 ppm (6380 mg/m$^3$) or 1800 ppm (3022 mg/m$^3$) in the same manner had offspring with no induced malformations.

Oral intubation of dams with 300 mg/kg acetonitrile was associated with a significant increase ($p<0.05$) in malformed offspring (rib and other axial

skeletal malformations). A significant increase ($p<0.05$) in fetal resorptions was also seen at the 300 mg/kg intubation level. Signs of toxicity were observed in the dams at this level, and one of six died. At the 200 mg/kg level, there were a number of fetal resorptions and at 100 mg/kg, two litters contained abnormal fetuses, with no signs of toxicity observed at either of these levels in the dams. In addition, there was a significant decrease in the average fetal body weight as compared with water intubated control animals. Intraperitoneal injections at the 400 mg/kg levels resulted in a limited number of abnormal offspring. with fetal resorptions and with encephalocoele, craniorachischisis or lumbosacral rachischisis, but these were not considered significant by the authors. A significant increase in fetal body weight was observed, but the relevance of this observation was not clear (Willhite, 1983).

No appropriate studies were available concerning chronic oral or inhalation exposure of acetonitrile to animals. Studies involving subchronic inhalation exposure in rats, dogs and monkeys (Pozzani et al., 1959a) have been done. Wistar rats were exposed to 0, 166 (279 mg/m$^3$), 330 (554 mg/m$^3$) or 655 ppm (1099 mg/m$^3$) acetonitrile vapor for 7 hours/day, 5 days/week for a total of 90 days. No significant changes were seen at the $\leq$330 (554 mg/m$^3$) level. In rats, transient histological changes in lung, liver and kidney were observed at the 655 ppm (1099 mg/m$^3$) level that were statistically significant when compared with controls.

In the subchronic inhalation study with rats, a NOAEL of 330 ppm (554 mg/m$^3$) and a LOAEL of 655 ppm (1099 mg/m$^3$) were determined, representing pulmonary, hepatic and renal effects in rats.

Adult male mixed-breed dogs were exposed to only one level, 350 ppm (558 mg/m³) for 91 days, and exhibited pulmonary abnormalities and transient depression of levels of hematocrit and hemoglobin.

Monkeys were exposed by inhalation to this same 350 ppm (558 mg/m³) level for 91 days. An additional series of monkeys were given 330 (554 mg/m³), 660 ppm (1108 mg/m³) or 2510 ppm (4214 mg/m³) for up to 99 days. Animals exposed to 330-350 ppm had focal dural or subdural hemorrhages of tissues adjacent to the superior saggittal sinus or slight to moderate hemorrhages of the superior or inferior saggital sinuses. Mild renal effects were also observed, and focal emphysema and proliferation of alveolar septa were also noted. Two of the three monkeys exposed to 350 ppm also had small discrete caseous nodules in the lungs. Neurological disorders were also observed in some of the animals.

In summary, exposure to acetonitrile vapor for 90 days caused adverse effects in dogs and monkeys at the 558 mg/m³ level. Effects in rats occurred at 1099 mg/m³ but not at 554 or 279 mg/m³. Statistically significant teratogenic and fetotoxic effects have been reported in hamsters after single oral doses as low as 300 mg/kg. At 100 mg/kg, fetal weight was significantly depressed. In rats, fetotoxic effects have been noted at 275 mg/kg/day, but not at 190 mg/kg/day, on days 6-19 of gestation.

Based on these data, rats appear to be less sensitive than dogs and monkeys to the general toxic effects of acetonitrile and less sensitive than hamsters to the teratogenic and fetotoxic effects of acetonitrile. An ADI for this compound could be derived from the rat NOEL of 279 mg/m³ but not from the rat NOEL of 554 mg/m³, because the latter value is very close to the 558 mg/m³ that caused lung, liver and kidney effects in monkeys. The

rat NOEL can be converted to an equivalent oral dose of 18.3 mg/kg/day (279 $mg/m^3$ x 0.22 $m^3$/day x 7 hours/24 hours x 5 days/7 days x 0.5 ÷ 0.35 kg). Applying an uncertainty factor of 1000 to account for less than lifespan exposure, species differences and sensitive subgroups, the ADI would be 18.3 µg/kg/day or 1.28 mg/day for a 70 kg man. This ADI could be extremely weak not only because of the uncertainties involved in route-to-route extrapolation and the inadequacy of the data on potential carcinogenicity, but also because the thresholds for subchronic toxicity have not been defined in dogs and monkeys and the threshold for fetotoxicity has not been defined in hamsters.

## 9. REPORTABLE QUANTITIES

### 9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Data regarding the effects of chronic exposure of animals to acetonitrile were not available, but effects of subchronic inhalation exposure of rats, dogs and monkeys were reported by Pozzani et al. (1959b). This study was used as a basis for the RQ in a previous determination (U.S. EPA, 1983); however, data (Willhite, 1983; IRDC, 1981) regarding teratogenic effects, which were previously unavailable, have become available. The subchronic inhalation and teratology studies were discussed in Sections 5.3. and 5.5. The data used to calculate MEDs and CSs are presented in Table 9-1. For the subchronic inhalation studies (Pozzani et al., 1959b), the inhalation exposures were converted to equivalent dosages by multiplying by 7 hours/24 hours and 5 days/7 days (to expand the exposure over a 24-hour day and a 7-day week) and by the animal daily inhalation volume, and by dividing by the animal body weight. An absorption efficiency of 100% was assumed. The inhalation volumes used were 0.223 $m^3$/day for rats, 1.5 $m^3$/day for dogs (Hertzberg and Dourson, 1983) and 1.24 $m^3$/day for monkeys (Guyton, 1947). The animal body weights used were 0.35 kg for rats, 14 kg for dogs and 3.5 kg for monkeys. The MEDs were calculated by multiplying the dose by the cube root of the ratio of the animal body weight to the weight of a human (70 kg) to correct for interspecies extrapolation and by 70 kg to express the MED in mg/day. The MED was divided by an uncertainty factor of 10 to approximate chronic exposure. The MEDs calculated as described differ from those in the previous RQ determination (U.S. EPA, 1983). The difference is due to a change in the methodology. In the former methodology, inhalation exposures were assumed to be equivalent among species, such that human doses were calculated directly, assuming 50% absorption efficiency and a human breathing volume of 20 $m^3$/day.

TABLE 9-1

Composite Scores Calculated from Subchronic Inhalation and Teratology Studies of Acetonitrile

| Route | Species | Dose/Exposure | Chronic Human MED (mg/day) | $RV_d$ | Effects | $RV_e$ | CS | RQ | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Inhalation | rat | 1099 mg/m³ 7 hours/day, 5 days/week for 90 days | 174.6* | 2.1 | Reversible pulmonary inflammation; renal and hepatic cloudy swelling (possibly focal cerebral hemorrhage) | 5 | 10.5 | 1000 | Pozzani et al., 1959b |
| Inhalation | dog | 581 mg/m³ 7 hours/day, 5 days/week for 90 days | 232.7* | 2.9 | Focal emphysema and proliferation of alveolar septa in lungs; transient depression of hematocrit and hemoglobin levels | 8 | 23.2 | 100 | Pozzani et al., 1959b |
| Inhalation | monkey | 554 mg/m³ 7 hours/day, 5 days/week for 90 days | 105.4* | 2.5 | Focal dural and subdural hemorrhages or mild to moderate hemorrhage in sagittal sinuses of brain, neurological disorders; pulmonary changes as in dogs but with small caseous nodules in lungs of 2 of 4; renal cloudy swelling | 8 | 20 | 1000 | Pozzani et al., 1959b |
| Inhalation | hamsters (pregnant) | 6380 mg/m³ 1-hour single exposure | 1633 | 1 | Teratogenic effects, severe axial skeletal (dysraphic) disorders | 10 | 10 | 1000 | Willhite, 1983 |
| Oral | hamsters (pregnant) | 200 mg/kg single dose | 23.9 | 3.4 | Same as above | 10 | 34 | 100 | Willhite, 1983 |
| Oral | rats (pregnant) | 275 mg/kg/day on days 6-19 of gestation | 47.0 | 3.0 | Fetotoxic effects, maternal mortality, reduced maternal weight | 8 | 24 | 100 | IRDC, 1981 |

*These values were divided by an uncertainty factor of 10 to estimate chronic exposure.

To calculate the MED for the inhalation teratology study in hamsters (Willhite, 1983), the exposure of 6380 mg/m³ was expanded over a 24-hour day, multiplied by the hamster daily breathing volume of 0.088 m³/day (Guyton, 1947), divided by the hamster body weight of 0.12 kg, and multiplied by the cube root of the body weight approximation and by 70 kg. The MEDs for the oral teratology studies in hamsters (Willhite, 1983) and rats (IRDC, 1981) were calculated by multiplying the dose by the cube root of the body weight ratios and by 70 kg.

The highest CS of 34 was obtained from the oral teratology study in hamsters and is the most appropriate basis for the RQ of 100 (Table 9-2).

## 9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Pertinent data for the calculation of these values were not located in the available literature as cited in the Appendix. According to the U.S. EPA (1984) guidelines this chemical should be place in Group D, since data are insufficient to allow any conclusion regarding carcinogenicity for humans.

TABLE 9-2

Acetonitrile
Minimum Effective Dose (MED) and Reportable Quantity (RQ)

| | |
|---|---|
| Route: | oral |
| Dose*: | 23.9 mg/day |
| Effect: | teratogenic effects in hamsters |
| Reference: | Willhite, 1983 |
| $RV_d$: | 3.4 |
| $RV_e$: | 10 |
| Composite Score: | 34 |
| RQ: | 100 |

*Equivalent human dose

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## APPENDIX

## LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in December, 1984, with the exception of TOXLINE, which was searched in March, 1984 and was kindly supplied by Dynamac Corp. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1984. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1984-1985. Cincinnati, OH. 116 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Vol.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technology Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1985. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

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U.S. EPA. 1983. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

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USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422. Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Service. Resource Publ. 137. Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California. State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. NTIS PB 269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.